

Idiopathic Anaphylaxis

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ABSTRACT

Anaphylaxis is an acute, life threatening event that can progress extremely rapidly. External allergens as causations have been identified over the last century. The most recently identified type of anaphylaxis is not caused by any external allergen and has been termed Idiopathic Anaphylaxis (IA). Two major types are Generalized or Angioedema with airway obstruction. IA is also classified by frequency of episodes and response to therapy. Therapy consists of acute emergency therapy and induction of remissions using prednisone, beta agonists, and H₁ blockers. Control and remission are usually induced. IA occurs at all ages, and pediatric and geriatric IA are often special problems, as is a psychogenic form where no true reactions occur. Although appropriate management of IA, in general, has a good prognosis, several problems exist. Among these are failure to accept IA as an entity or in an individual case by physicians and patients. A different problem occurs when the recommended treatment is used and there is control of IA, but only with persisting high doses of prednisone. This is corticosteroid dependent IA. The lack of defined mechanisms that will lead to improved therapies and wider acceptance of IA as an entity remains a major problem. Undifferentiated Somatoform IA is a serious management problem for physicians. (Allergy and Asthma Proc 20:311-315, 1999)

Anaphylaxis is a generalized allergic reaction and a medical emergency that can result in death within minutes. A classification of anaphylaxis is shown in Table I.

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HISTORICAL ASPECTS

IgE mediated anaphylaxis was first documented in 2641 B.C., when King Menses was stung to death by a wasp or hornet according to hieroglyphics.¹ The first scientific description of anaphylaxis was in dogs, secondary to an allergic reaction to toxin from a sea anemone.² As allergenic substances became available, such as horse serum used as an antitoxin, reports of anaphylaxis occurred, and penicillin was identified as a major problem in the mid 20th century. Thus, the allergen had to be available for anaphylaxis to that agent to be described.

Idiopathic Anaphylaxis (IA) was first described in 1978.³ A point to consider is that anaphylaxis to hymenoptera stings was first apparent in 2641 B.C., but correlation of food anaphylaxis was not defined until early in the 20th century and was initially termed food "poisoning."⁴ Thus, food anaphylaxis (like hymenoptera anaphylaxis) probably existed for thousands of years. Similarly, it can be postulated that IA did not have its onset in the last quarter of this century, but occurred for thousands of years without recognition of what the disease was. Unfortunately, the diagnosis is frequently missed even at the present time.

CLASSIFICATION OF IA

As increasing numbers of cases of IA were seen, it became possible to classify the cases in terms of major clinical presentation, i.e., Generalized (G) or life threatening Angioedema (A). Further, the frequency of episodes were classified as frequent (F) or infrequent (I). The current classification of IA is shown in Table II.

TREATMENT OF IA

As increasing numbers of cases of IA were seen, both acute and preventative treatment regimens were designed and used. These were initially based on regimens used to prevent radiographic contrast media reactions⁵ and are shown in Figure 1. These treatment regimens were shown to be effective.^{6,7} The outcome of these treatment regimens is diagrammed in Figure 2.

In general, the outcome of treatment of IA has a good prognosis. Most patients are off prednisone within 1 year of

TABLE I

Classification of Anaphylaxis

Type	Mechanism	Examples of Causes
IgE mediated anaphylaxis	Antigen reacts with IgE antibody on mast cells	Foods, insect venoms, drugs, foreign serum, latex, allergen injections
Anaphylactoid	A. Opiates B. Radiographic contrast media	A. Direct stimulation of mast cells B. Mechanism unknown
Exercise induced	Uncertain	Running causes anaphylaxis
Food and exercise induced	Uncertain	A specific food plus exercise results in anaphylaxis
Idiopathic anaphylaxis (IA)	Uncertain	Sudden spontaneous onset of generalized anaphylaxis or life threatening angioedema
Undifferentiated somatoform IA (USIA)	Psychogenic	Patient describes symptoms of IA but these are never objectively documented

TABLE II

Classifying Idiopathic Anaphylaxis (IA)

Disease	Symptoms
Generalized (G)	Urticaria or angioedema with bronchospasm, hypotension, syncope
Angioedema (A)	Angioedema with upper airway compromise (laryngeal, pharyngeal, tongue)
Frequency of episodes	More than 6 times per year: frequent (F) Less than 6 times per year: infrequent (I)
Summary of diagnoses	IA-G-F, IA-A-F, IA-G-I, IA-A-I

Variations of IA Diagnoses

Corticosteroid dependent IA (CSD-IA)	Applied when a patient is controlled by prednisone, but has recurrent episodes of IA below a threshold dose of prednisone
Malignant IA (M-IA)	Applied when a patient requires high doses of prednisone to control IA. The doses of prednisone were arbitrarily set at 30 mg daily or 60 mg on alternate days, but much higher doses may be required.
IA-Questionable (Q)	Applied for a patient with possible IA where documentation of objective findings are unsuccessful and diagnosis is uncertain.
IA-Variant (V)	Applied when symptoms of IA vary from classic IA. IA-V may subsequently be classified as IA-A, IA-G, IA-Q, or USIA.
Undifferentiated somatoform IA (USIA)	Symptoms mimic IA but not objective findings are documented, and the symptoms are not responsive to the regimen for IA.

initiation of treatment. This is in contrast to the outcome of patients with severe prednisone dependent asthma.

SPECIAL PROBLEMS IN IA

Undifferentiated Somatoform IA

This diagnosis defines patients who have a psychiatric disease and express this by reporting symptoms that appear to be IA.⁸ The diagnosis is one of exclusion by failure to find objective evidence of documentation of physical findings consistent with IA in Emergency Service ex-

aminations and usually failure to respond to the regimen for IA. The prognosis is poor as the concept of psychiatric disease is rejected by the patient and sometimes by the personal physician. These patients may be treated with excess doses of prednisone with the expected side effects.

Pediatric IA

There is a lower incidence of IA in the pediatric population, but this does occur and is frightening to patients and families.^{9,10} Fortunately, the pediatric IA cases

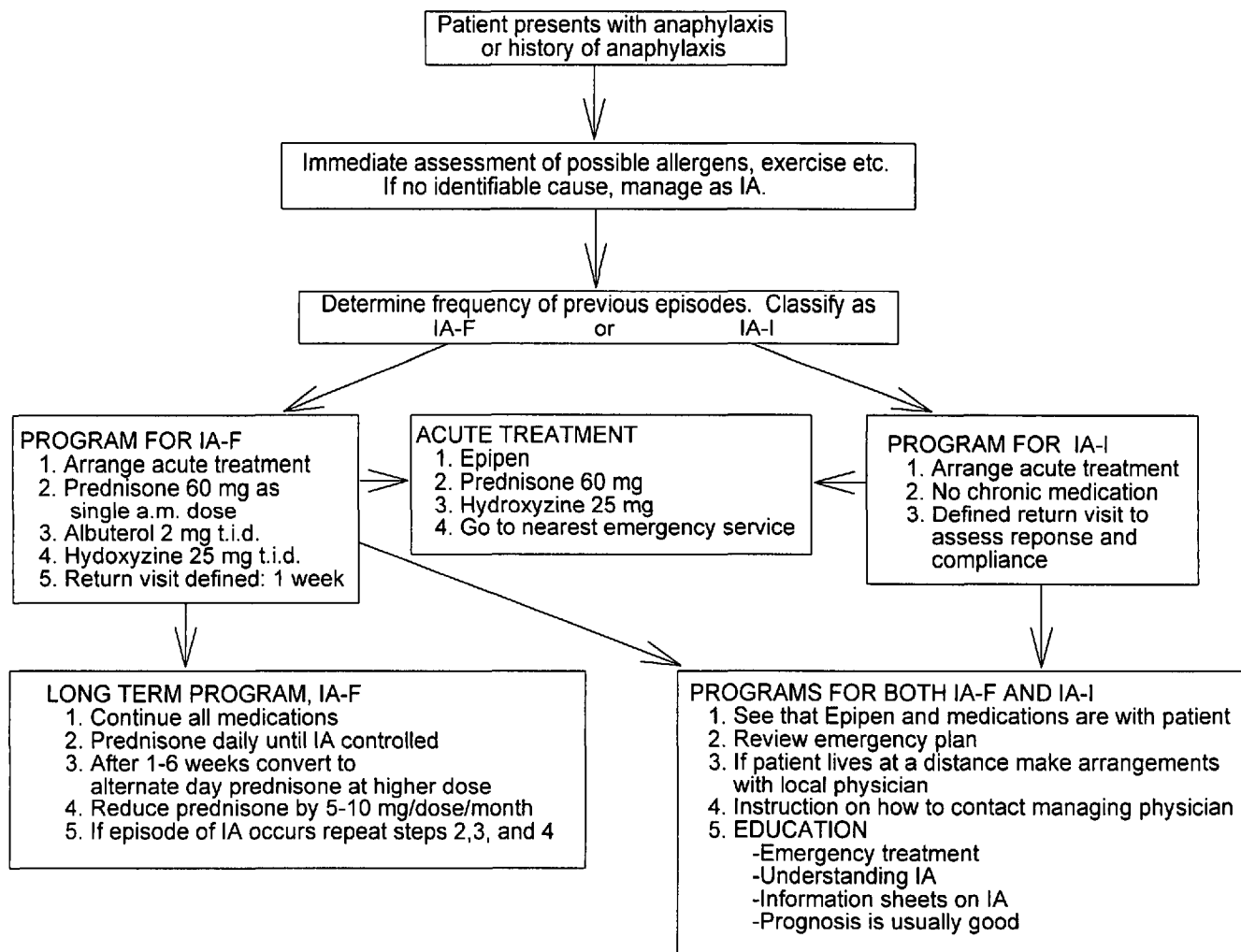


Figure 1. Algorithm for the management of idiopathic anaphylaxis. From Patterson R, Harris KE. Classification of idiopathic anaphylaxis (IA) and an algorithm for the management of IA. In Patterson R. (Ed.) *Idiopathic Anaphylaxis*. Providence, RI: Oceanside Publications, 22, 1997.

respond to the same regimen developed for adult cases of IA, with appropriate adjustment of doses for body weight.

Fatalities from IA

Fatalities have been reported¹¹ and it is very likely that far more fatalities have occurred than have been reported because of failure to describe the disease for decades (or centuries as described in the introductory statements) and failure to make the diagnosis even at the present time.

Corticosteroid Dependent IA

This refers to patients whose prednisone dosage cannot be lowered below a certain threshold. Zaditen (ketotifen), a mast cell stabilizer not available in the U.S., is helpful in many such cases.¹²

Patient Education

Patients with IA, and at times the referring physician, may not accept the diagnosis and lack of an external allergen as a triggering event. Further, the use of prednisone

alarms some patients and their personal physicians. For these reasons we published a book on IA, from which we receive no royalties, so that a comprehensive source of information was available to patients and their physicians.¹³

Potential Mechanisms of IA

These have been discussed in detail by Grammer.¹⁴ The explanation for IA reactions is unknown, and it may be decades before the mechanisms are established for IA-G and IA-A. These two types of IA may differ in the mechanisms responsible. Possible mechanisms to be considered are as follows. An autoimmune mechanism such as IgG antibodies against IgE fixed to mast cells or IgG antibodies against the IgE receptor on mast cells are both possible mechanisms. The action of histamine releasing factors is another mechanism to be studied. A major problem in evaluating mechanisms is that patients with IA-F must have treatment started immediately to prevent fatalities, and the mechanism responsible for IA may be altered by the IA therapeutic regimen.

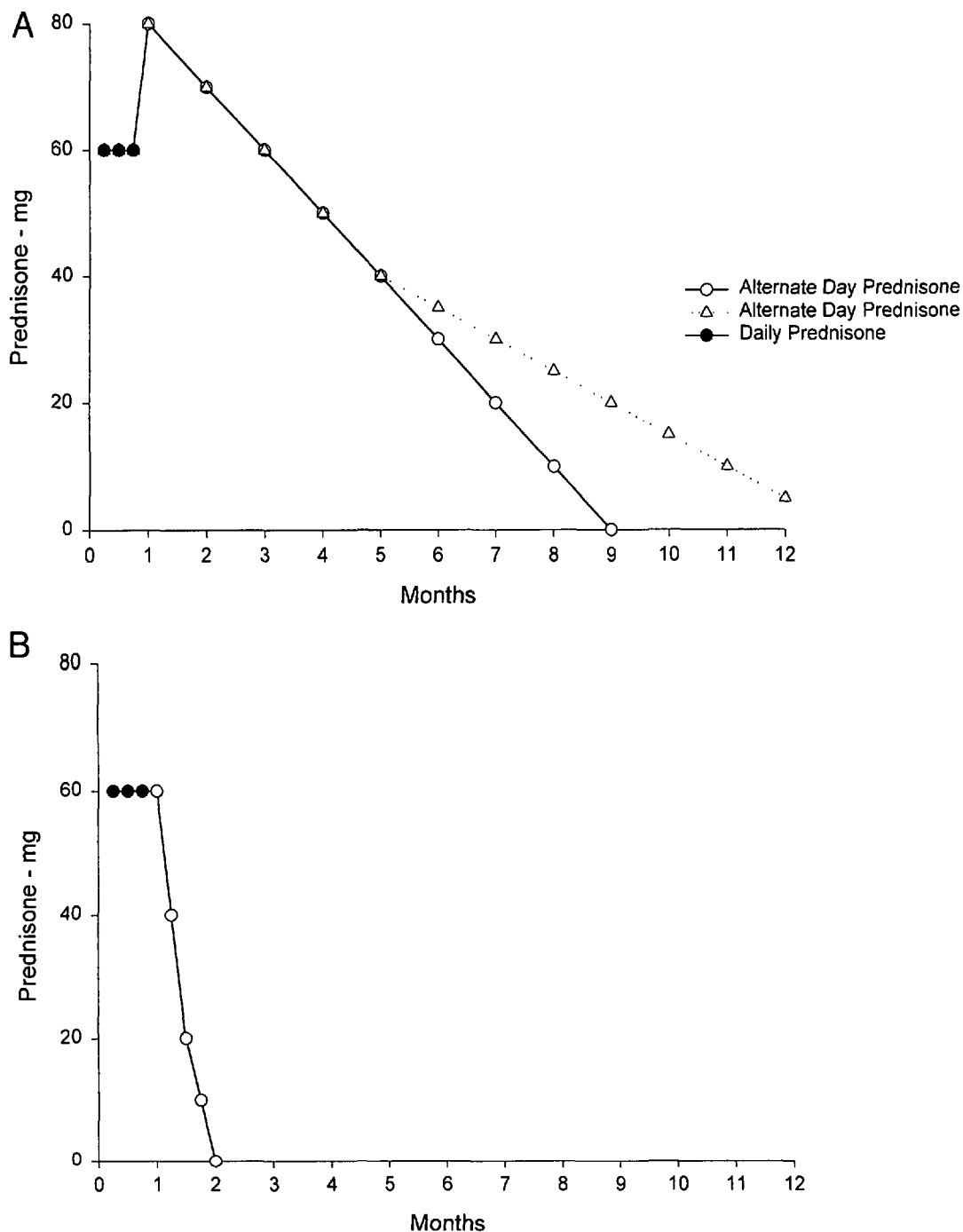


Figure 2. Two outcomes of therapy for IA-G-F. A. Daily prednisone is converted to alternate day prednisone, reduced, and discontinued. The rate of prednisone reduction depends upon the history, experience, and judgment of the physician. B. Prednisone does not control episodes and no objective evidence of IA is documented. Rapid reduction and discontinuation of prednisone is carried out as the patient has undifferentiated somatoform IA. From: Patterson R, Harris KE. Patterns of response to management of idiopathic anaphylaxis and ketotifen in management of idiopathic anaphylaxis. In Patterson R. (ed.) *Idiopathic Anaphylaxis*. Providence, RI: Oceanside Publications, 35, 1997.

REFERENCES

- McGrath KG. Anaphylaxis. In: *Allergic Diseases: Diagnosis and Management*, 5th ed. Patterson R, Grammer LC, Greenberger PA (Eds). Philadelphia: Lippincott-Raven, 439-458, 1997.
- Portier P, Richet C. De l'action anaphylactique de certaines venins. *Compt Rend Soc Biol* 54:170-172, 1902.
- Bacal E, Patterson R, Zeiss CR. Evaluation of severe (anaphylactic) reactions. [Clin Allergy 8:295-304, 1978.](#)
- Cohen SG. Landmark Commentary: Smith, Cole, Thayer and the scratch test. *Allergy Proc* 11:189-192, 1990.
- DeSwarte RD, Patterson R. Drug Allergy. In: *Allergic Diseases: Diagnosis and Management*, 5th ed. Patterson R, Grammer LC, Greenberger PA (Eds). Philadelphia: Lippincott-Raven, 317-412, 1997.
- Wiggins CA, Dykewicz MS, Patterson R. Idiopathic anaphylaxis: Classification, evaluation, and treatment of 123 patients. [J Allergy Clin Immunol 82:849-855, 1988.](#)

7. Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R. Idiopathic anaphylaxis: A series of 335 cases. [Ann Allergy Asthma Immunol 77:285–291, 1996.](#)
8. Choy AC, Patterson R, Patterson DR, Grammer LC, Greenberger PA, McGrath KG, Harris KE. Undifferentiated somatoform idiopathic anaphylaxis. [J Allergy Clin Immunol 96:893–900, 1995.](#)
9. Ditto A, Krasnick J, Greenberger PA, Kelly KJ, McGrath K, Patterson R. Pediatric idiopathic anaphylaxis: Experience with 22 patients. [J Allergy Clin Immunol 100:320–326, 1997.](#)
10. Hogan MB, Kelly MA, Wilson NW. Idiopathic anaphylaxis in children. [Ann Allergy Asthma Immunol 81:140–142, 1998.](#)
11. Patterson R, Clayton DE, Booth BH, Greenberger PA, Grammer LC, Harris KE. Fatal and near fatal idiopathic anaphylaxis. [Allergy Proc 16:103–108, 1995.](#)
12. Patterson R, Harris KE. Patterns of response to management of idiopathic anaphylaxis and ketotifen in management of idiopathic anaphylaxis. In: *Idiopathic Anaphylaxis*. Patterson R (Ed.). Providence: Oceanside Publications, Inc., 33–44, 1997.
13. Patterson R (Ed). *Idiopathic Anaphylaxis*. Providence: Oceanside Publications, Inc., 1997.
14. Grammer LC. Potential mechanisms of idiopathic anaphylaxis. In: *Idiopathic Anaphylaxis*. Patterson R (Ed). Providence: Oceanside Publications, Inc., 59–64, 1997. □